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Mathieu Corvaisier, Antoine Brangier, Cédric Annweiler, Laurence Spiesser-Robelet

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## Review

## Preventable or potentially inappropriate psychotropics and adverse health outcomes in older adults: systematic review and meta-analysis



Corvaisier Mathieu<sup>a,b,c,d,\*</sup>, Brangier Antoine<sup>c</sup>, Annweiler Cédric<sup>b,c,e,f</sup>,  
Spiesser-Robelet Laurence<sup>a,d,g</sup>

<sup>a</sup> UNIV ANGERS, School of Pharmacy, Health Faculty, University of Angers, 49045 Angers, France

<sup>b</sup> UNIV ANGERS, EA4638, University of Angers, 49100 Angers, France

<sup>c</sup> Department of Geriatric Medicine, Research Center on Autonomy and Longevity, University Hospital, 49933 Angers, France

<sup>d</sup> Department of Pharmacy, Angers University Hospital, 49933 Angers, France

<sup>e</sup> UNIV ANGERS, School of Medicine, Health Faculty, University of Angers, 49045 Angers, France

<sup>f</sup> Gerontopôle of Pays de la Loire, 44000 Nantes, France

<sup>g</sup> EA 3412 Health Education and Promotion Laboratory, University of Sorbonne Paris Nord, 93017 Bobigny, France

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## ABSTRACT

**Objective:** To systematically review and quantitatively synthesize evidence on the use of PIPs linked to adverse health outcomes in older adults.

**Methods:** A Medline, Embase<sup>®</sup> and OpenGrey libraries search was conducted from 2004 to February 2021, using the PICO model: older people, psychotropic drugs, inappropriate prescribing, and adverse drug events. Fixed-effects and random-effects meta-analysis were performed from 3 eligible studies using an inverse-variance method.

**Results:** Of the 1943 originally identified abstracts, 106 met the inclusion criteria and 7 studies were included in this review. All were of good quality. The number of participants ranged from 318 to 383,150 older adults (54.5–74.4% women). Associations were found between PIPs use and decreased personal care activities of daily living (ADL), unplanned hospitalizations, falls and mortality. In the pooled analysis, association with falls was confirmed (1.23 [95%CI: 1.15;1.32]).

**Conclusions:** Participants of 65 years and older treated with PIPs were more at risk of adverse health outcomes than those using no PIPs, including greater risks of falls, functional disabilities, unplanned hospitalizations, and mortality. Results of the present systematic review and meta-analysis provide additional evidence for an appropriate and safe use of psychotropics in older adults.

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## 1. Introduction

Older adults are particularly vulnerable to iatrogenic events and their adverse health outcomes. About 16% of older hospitalized patients are exposed to adverse drug reactions [1]. Preventable adverse drug reactions that lead to the hospitalization in older adults rise to 63% according to a recent meta-analysis [2]. It is also very important to use medications safely, especially potentially inappropriate medications (PIMs). PIMs may be defined as medications associated with a high risk of adverse health outcomes [3]. Several lists of PIMs have been developed to identify medications at risk in older adults, such as European list (EU(7)-PIM list [4], STOPP/START list [5] or American list as the criteria by

Beers et al. [6] and updates [7–10]. Among those PIMs, psychotropics (ie, antipsychotics, antidepressants, anxiolytics, hypnotics, and antimanic drugs) are widely mentioned. A recent meta-analysis mentioned that psychotropics contributed to 2.1% of hospitalizations and 11.3% of adverse drug event-related hospitalizations [11]. Psychotropics are associated with several adverse health outcomes such as fall [12], cognitive decline [13] and mortality [14]. Although iatrogenic effects of psychotropics are well-described, the literature remains poor on potentially inappropriate psychotropics (PIPs). The purpose of this systematic review and meta-analysis was to systematically review and quantitatively synthesize evidence on the use of PIPs linked to adverse health outcomes in older adults.

\* Corresponding author.

E-mail address: [mathieu.corvaisier@chu-angers.fr](mailto:mathieu.corvaisier@chu-angers.fr) (M. Corvaisier).

2. Methods

2.1. Literature search

Studies were identified through systematic searches of the databases including PubMed (NLM), EMBASE (Ovid), and OpenGrey as well as other relevant databases from 2004, date of first guidelines about psychotropics, through February 2021. A comprehensive search strategy was designed using medical subject headings (MeSH) and free text terms by our research team in consultation with a senior librarian. We included English-language and French-language peer-reviewed research studies and those concerned population aged over 65 and 80. The research equation was a combination of 4 term blocs according to the PICO model: older people, psychotropic drugs, inappropriate prescribing, and adverse drug events (Appendix 1). An iterative process was used to ensure all relevant articles had been obtained. A further hand search of bibliographic references of extracted papers and existing reviews was also conducted to identify potential studies not captured in the electronic

database searches. The quality of each study was assessed independently by two reviewers (MC and LSR) using the 'Crombie criteria' [15] adapted by Petticrew and colleagues [16].

2.2. Study selection and analysis

Two independent reviewers (MC and LSR) independently identified studies considering inclusion and exclusion criteria based on title, abstract and full-text review into Rayyan QCRI<sup>®</sup>. Initial screening criteria for the abstracts were: (1) quantitative studies, (2) referred to an inappropriate prescribing of psychotropics as an overprescribing, a prescribing error (wrong dosage, wrong duration, wrong timing), an under prescribing, that means a drug related problem which could have been avoided, (3) referred to adverse drug events as side effect, a length of hospitalization increasing, a rehospitalization, a transitional or permanent disability or a death (4) referred to psychotropics as antidepressants, antimanic drugs, anxiolytics, hypnotics, or antipsychotics and, (5) with participants aged 65 or older. If a study met the initial selection criteria or

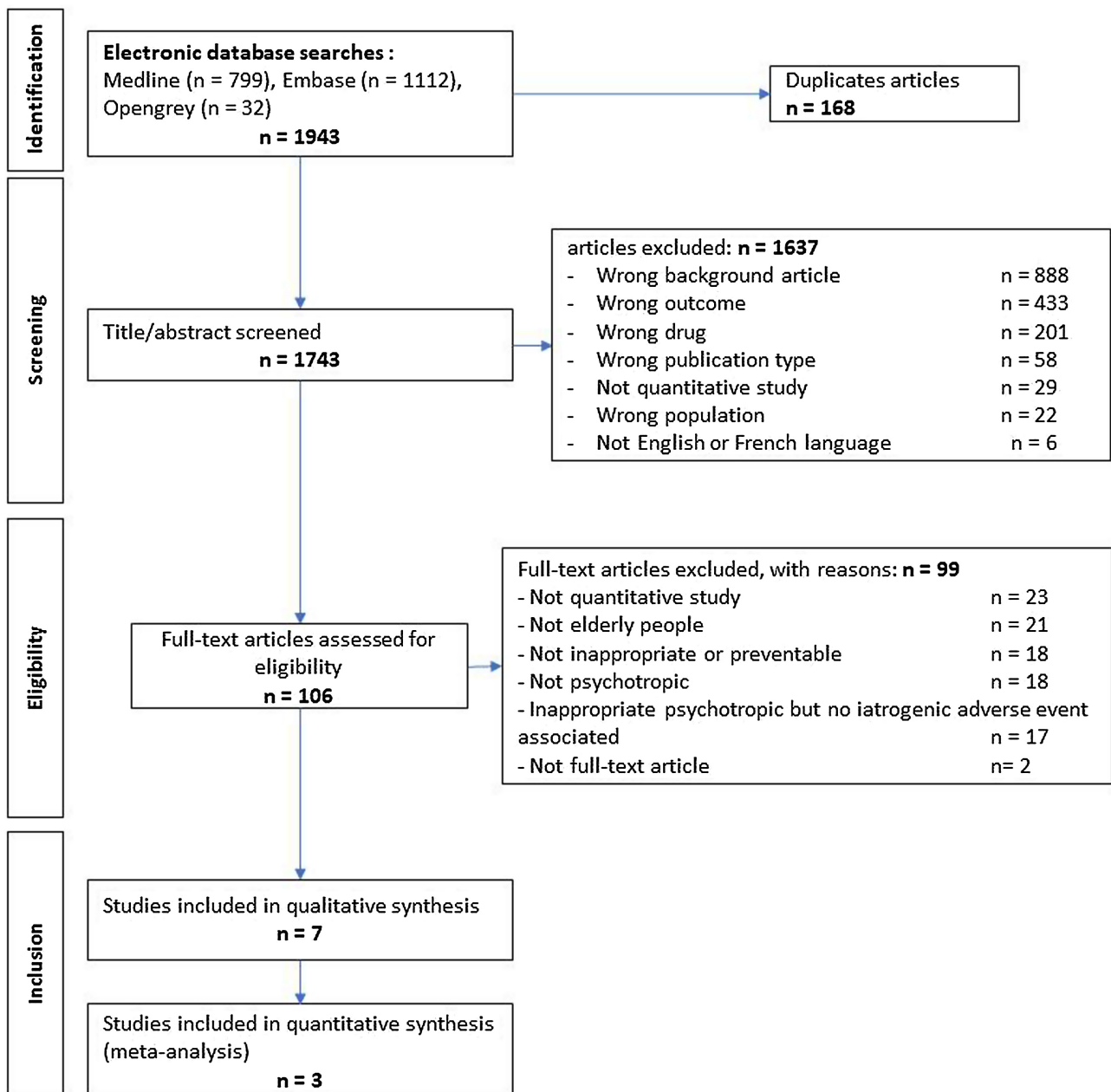


Fig. 1. Flow diagram of selection of studies focusing on potential inappropriate psychotropics and iatrogenic adverse events in older adults.

its eligibility could not be determined from the title and abstract, the full text was retrieved. Disagreements regarding the study selection process and data extraction, was resolved by consensus. A third reviewer (CA) was invited if further consultation was required to obtain an agreement. If three or more studies reported similar outcome measures, a meta-analysis of the data was planned. The study selection is shown on a flow diagram (Fig. 1).

Of the 1943 originally identified abstracts, 106 met the initial inclusion criteria (Appendix 2). Following thorough examination, we excluded 99 of those 106 studies because any quantitative data were available (n = 25), no data were available for older people (n = 21) or psychotropics (n = 18), data did not concerned inappropriate or preventable psychotropics (n = 18) or no health outcomes were associated with inappropriate psychotropics (n = 17), and references were not full-text article (n = 2). The remaining 7 studies were included in this review [17–23]. Extracted information for each study included information such as author name, date of publication and country, population's demographic detail (mean age and study structure), sample size, psychotropics concerned, inappropriate drugs list used if applicable, outcome measure and outcome of interest (Table 1).

2.3. Definition of outcomes

We examined if an association was described between an inappropriate psychotropic drug used (antidepressants, antimanic drugs, anxiolytics, hypnotics, antimentia and/or antipsychotic) and a health outcome. Health outcomes corresponded to any event occurring during the study period, which could be an adverse event, an increase in the length of hospitalization, a rehospitalization, a transitional or permanent disability or death. Inappropriate used was defined as an overprescribing, a prescribing error (wrong dosage, wrong duration, wrong timing), an under prescribing or a potential inappropriate medication as defined in Beers' criteria or other similar lists.

2.4. Meta-analysis

A quantitative meta-analysis was performed for all outcomes targeted by at least 3 studies retrieved in the systematic review. If the number of studies is below 3, there is a risk of: (i) imprecise estimate of impact; (ii) accumulated risk of bias; (iii) lack of power to detect a real effect; (iv) risk of instability of the results; and (v) difficulty to assess heterogeneity. Of the 7 articles selected, only the adverse fall outcome was present in at least 3 articles [17,18,22]. When applicable, adjusted odds ratio (OR) or hazard ratio (HR) and 95% CI were extracted. A fixed-effects and random-effects meta-analysis were performed on the estimates to generate summary values (Review Manager version 5.1, The Nordic Cochrane Centre, Copenhagen, Denmark). Results are presented as forest plots. Heterogeneity between studies was assessed using Cochran's Chi-squared test for homogeneity (Chi2), and amount of variation due to heterogeneity was estimated by calculating the I<sup>2</sup> [24]. Our systematic review and meta-analysis followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Appendix 3).

3. Results

3.1. Study characteristics

Table 1 summarizes the 7 studies included in this review [17–23] and were of good quality (Appendix 4). The research process identified no previous literature review on this issue specifically. Five studies were conducted in Europe (including 3 in France) [18–22], one in North America [17] and one in Oceania [23]. The number of participants ranged from 318 [21] to 383,150 [23]. All participants were 65 years old or older and 3 studies presented mean age over 80 [17,19,21], with 54.5% [19] to 74.4% women [17]. Participants lived in community-dwelling [17,22],

**Table 1**  
Summary of included studies, sorted by adverse health outcome.

Author, year, country	Design	Setting/participants, age	Psychotropics concerned	Inappropriate drugs list used	Adverse health outcome	Outcome of interest	Confounding factors
Agashivala and Wu, 2009, USA [17]	Retrospective study based on a national health database	- Location: USA - n = 11,940 community-dwellers in 1174 facilities, mean age = 84.1 y, 74.4% female	Psychotropic drugs (sedatives, hypnotics, anti-anxiety agents, antipsychotics, antidepressants, anorexiant, antiemetics, sleep-aid products and other medications for central nervous system and Alzheimer-type dementia)	Beers' criteria (2003)	Fall over the past 30 days following analysis. Nursing staff declaration.	Potentially inappropriate psychotropics increased risk of falling compared with appropriate psychotropics OR = 1.205 (1.020–1.424) p = 0.028 Potentially inappropriate psychotropics increased risk of falling compared with not receiving psychoactive medications OR = 0.624 (0.516–0.754) p < 0.001 (logistic regression analysis)	Age, gender, ethnicity, appropriate psychoactive medications, non-psychoactive medications, mental disorders, mood indicators, number of impaired ADLs, bedralls, fall history (31–180 days)
Berdot et al., 2009, France [18]	Prospective cohort study	- Location: France - n = 6,343 non-institutionalized participants in 3 hospital centers, aged ≥ 65 y, mean age = 73.7 y, 59.0% female	Long-acting benzodiazepines Psychotropic drugs Occasional or regular using	Beers' criteria (2003) and Laroché	At least one fall during the 4-year follow-up. Participant declaration.	Potentially inappropriate Long-acting benzodiazepines increased risk of falling compared with never used inappropriate medication Occasional user : OR = 1.40 (1.10–1.79) p = 0.006 Regular user : OR = 1.41 (1.12–1.79) p = 0.004 Potentially inappropriate psychotropics increased risk of falling compared with never used inappropriate psychotropics Occasional user : OR = 1.17 (0.74–1.783) p = 0.5 Regular user : OR = 1.74 (1.14–2.66) p = 0.01 (logistic regression analysis)	Age, gender, study center, Body Mass Index, diurnal drowsiness, number of drugs, cognitive functioning, depressive symptoms, impaired mobility

(continued on next page)

Table 1 (continued)

Author, year, country	Design	Setting/participants, age	Psychotropics concerned	Inappropriate drugs list used	Adverse health outcome	Outcome of interest	Confounding factors
Hyttinen et al., 2019, Finland [22]	Retrospective longitudinal study based on a national health database	- Location: Finland - n = 20,666 community-dwellers, aged ≥65 y, mean age = 74.6 y, 62.4% female	Psychotropic drugs	Finnish Meds 75 + database (2010)	Fall-related incident fracture during psychotropics exposure. Finnish version of ICD declaration.	Potentially inappropriate psychotropics increased risk of fracture: - At 1 month of psychotropics exposure 1.23 (1.14–1.33) p < 0.001 - At 3 months of psychotropics exposure 1.22 (1.13–1.32) p < 0.001 - At 6 months of psychotropics exposure 1.22 (1.13–1.32) p < 0.001 (extended Cox model for proportional hazards)	Age, gender, socioeconomic status, living situation, morbidity, excessive polypharmacy
Adverse health outcome: mortality							
Bo et al., 2018, Italy [19]	Prospective cohort study	- Location: Northern Italy - n = 896 hospital-discharged patients in 2 hospital centers, aged ≥65 y, mean age = 81.9 y, 54.5% female - Only patients who had a disease group	Antipsychotics drugs	Beers' criteria (2015)	Mortality at 6 months. Patients or usual caregivers' declaration.	Potentially inappropriate antipsychotics drug increased risk of death compared with do not use OR = 1.65 (1.12–2.44) p = 0.01 (Multivariate Odds Ratio)	ADL loss of function, frailty according CSHA (Canadian Study of Health and Aging) scale, respiratory diseases, digoxine dosage >0.125 mg/daily, aspirin for primary prevention of cardiac events
Hiance-Delahaye et al., 2018, France [21] SIPAF study	Cross-sectional study	- Location: France - n = 318 antidepressant users among 2,350 people selected at random among recipients of a French supplementary pension fund, aged ≥65 y, Mean age = 84.0 y, 71.1% female	Antidepressants	Beers' criteria (2015)	Mortality at 6 months. insurance company declaration.	Potentially inappropriate antidepressants increased mortality compared with appropriate antidepressants HR = 2.30 (1.28–4.12) p = 0.005 (logistic regression analysis)	Age, gender, hospitalization un the prior 6 months, cognitive impairment, level of dependency, number of chronic diseases, polypharmacy, nutritional impairment, depressive syndrome
Adverse health outcome: Unplanned hospitalizations							
Price et al., 2014, Australia [23]	Retrospective study based on national health data-bases. Case-time-control design.	- Location: Western Australia - n = 383,150 hospitalized index subjects, aged ≥65 y, 55.5% female	- Antipsychotics (thioridazine) n = 79,914 - Anxiolytics, hypnotics/sedatives (oxazepam, alprazolam, diazepam, temazepam) n = 60,497 - Antidepressant (amitriptyline, doxepin, fluoxetine) n = 90,128	Beers' criteria (2003)	Unplanned hospitalizations during 9-year follow-up. Information from the Western Australia Data Linkage System.	Potentially inappropriate psychotropics association with unplanned hospitalizations : Thioridazine OR = 1.35 (1.11–1.63), significant Oxazepam OR = 1.22 (1.15–1.30), significant Alprazolam OR = 1.16 (0.94–1.43) Diazepam OR = 1.26 (1.18–1.34), significant Temazepam OR = 1.27 (1.21–1.34), significant Amitriptyline OR = 1.07 (0.99–1.14) Doxepin OR = 1.01 (0.92–1.12) Fluoxetine OR = 1.07 (0.93–1.22) (logistic regression analysis)	Others potentially inappropriate medications
Adverse health outcome: Personal care activities modified							
Fond et al., 2016, France [20]	Cross-sectional study	- Location: Marseille, France - n = 327 hospitalized patients in 13 psychiatric hospital centers, aged ≥65 y, Mean age = 73.9 y, 62.1% female	Psychotropic drugs (antipsychotics; antidepressants; anxiolytics)	Beers' criteria (2003)	Personal care activities modified, measured by ADL scale by nurses during hospitalization.	Potentially inappropriate psychotropics decreased personal care activities compared with do not use Potentially inappropriate psychotropics. OR = 0.88 (0.79–0.97) p = 0.01 (Multivariate Odds Ratio)	Age, gender, psychiatric and somatic diagnoses

CIRS: Cumulative Illness Rating Scale; ICD: International Classification of Diseases; ADL: activities of daily living.

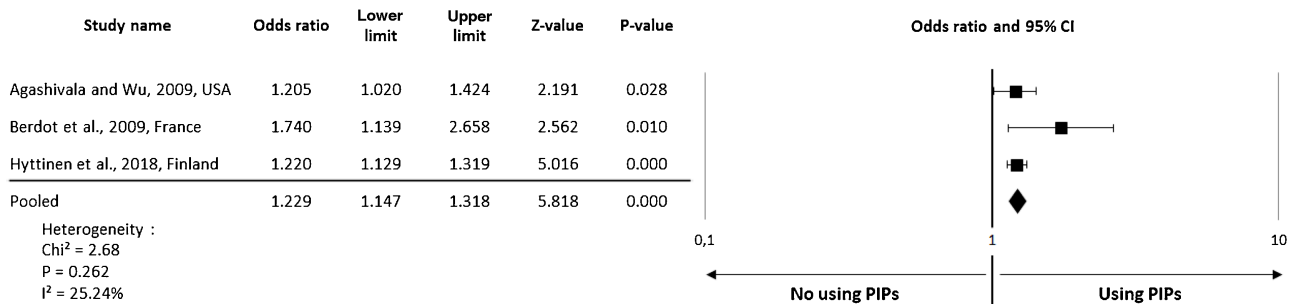


Fig. 2. Meta-analysis of studies on potentially inappropriate psychotropics and fall.

PIPs: Potential Inappropriate Psychotropics. Horizontal lines correspond to the 95% confidence interval (CI). Black diamond represents the summary value in fixed effects analysis. The bold vertical line corresponds to an odds ratio of 1.0, equivalent to no association.

at home [18] or were evaluated during hospitalization [20,23] or during hospital discharge [19]. All psychotropics were focused in 4 studies [17,18,20,22] whereas antipsychotics were focused in one study [19], antidepressants in one study [21], long-acting benzodiazepines in one study [18] and certain molecules of the class of antipsychotics, antidepressants or anxiolytics and sedatives in one study [23]. Inappropriate psychotropics were determined using Beer's criteria updating in 2003 [17,18,20,23], Beer's criteria updating in 2015 [19,21] or a Finnish national list [22]. Health outcomes focused were fall [17,18], fall-related fracture [22], decrease of personal care activities [20], unplanned hospitalization [23] or mortality [19,21]. In all studies, regression models were performed considering potential confounders, which varied between studies (age, gender, body mass index, ethnicity, study center, polypharmacy, appropriate psychotropics, non-psychotropic drug, other potentially inappropriate medications, mental or cognitive impairments, mood indicators, or number of chronic diseases). Finally, three of seven studies could contribute to a meta-analysis because evaluating the association between the use of PIPs and the onset of accidental falls or fall-related fractures [17,18,22].

### 3.2. Inappropriate psychotropics and falls

Three of seven studies examined association between psychotropics and falls. All of them found that the use of PIPs significantly increased the risk of fall compared to using no PIPs [17,18,22]. One study also found that a similar result compared to using appropriate psychotropics [17]. When compiling all available results [17,18,22], the summary odds ratio in fixed effects was 1.23 [95%CI: 1.15;1.32] ( $\text{Chi}^2 = 2.68$ ,  $P = 0.262$ ;  $I^2 = 25.24\%$ ), suggesting a direct association of the use of PIPs with fall risk (Fig. 2). The pooled OR in random-effects meta-analysis was 1.24 [95%CI: 1.12;1.37]. Some causes of heterogeneity were identified: participants lived in community-dwelling [17,22] or at home [18]; benzodiazepine used [18] or psychotropics used [17,22]; 2003 beers' criteria used [17,18] or Finnish national list [22]. There was a reporting bias according to response rates (90% [17] vs 37% [18] vs 10% [22]).

### 3.3. Inappropriate psychotropics and other health outcomes

An increased mortality risk was retrieved with the use of antipsychotics [19] and antidepressants [21]. The first study evaluated mortality up to 6 months, and the second one up to two years. Another study also showed that the use of PIPs in older inpatients with psychiatric disorders was associated with decreased personal care activities of daily living (ADL) compared to using no PIPs [20]. Finally, one study found an association of various psychotropics (thioridazine, oxazepam, diazepam and temazepam) with an increased risk of unplanned hospitalizations [23].

## 4. Discussion

This systematic review and meta-analysis provides evidence that potentially inappropriate psychotropics are associated with the onset of

various negative health outcomes, notably greater risks of accidental falls, reduced functional abilities and unplanned hospitalizations.

Our results indicated a 'large' association between using PIPs and fall risk compared to using no PIPs, in community-dwellers and non-institutionalized participants (Fig. 2). Association between psychotropics use and adverse health outcomes is well-described, but some data suggest that using appropriate psychotropics is significantly less harmful than using PIPs [17,21]. This is especially obvious when considering a regular use of at least 2 years in a row [18], although the difference is more subtle with a psychotropic exposure of less than 6 months [22]. In a dynamic of reducing the use of PIPs, this suggests that first aim is to prevent psychotropics use before 2 years and focusing on deprescription of PIPs beyond 2 years could be prioritized. Among the studies selected in this review, one included a very large population allowing to have results about some molecules among the PIPs associated with unplanned hospitalization [23]. Within the same therapeutic class, some molecules were associated with a higher rate of unplanned hospitalization compared to others. It could be interesting to distinguish between different PIPs within the same therapeutic class to give preference to those identified as being of lower risk. Finally, the majority of PIMs list used were the Beers criteria, as well as the French Laroche list [25] and the Finnish meds75+ database [26]. Similar studies should be conducted with new, recently updated European international lists such as the EU (7)-PIM list [4] and the STOPP/START list [5]. The findings of our systematic review and meta-analysis need to be tempered by several limitations. First, this is a relatively new and emerging area of research, and only a limited number of studies have been conducted to date, which narrowed the number of studies to be included in this systematic review and meta-analysis. Therefore, our conclusions need to be confirmed in larger and preferably prospective studies. Second, it is possible that the heterogeneity and relatively small size of some studied samples may have exposed the analysis to a lack of statistical power with the risk of missing significant differences of adverse health events according to the use of PIPs. Third, the duration of psychotropic exposure was not reported in all selected studies, although the length of exposure appears to be an important factor to consider. Fourth, it is possible that the use of the most recent 2019 update of Beer's criteria may have yielded slightly different results compared to the 2003 update which was mainly used in selected studies. Fifth, the three studies selected in our meta-analysis did not assess the same fall outcome. Harmonization of outcome measures seems thus desirable. Finally, some potential limitations of the meta-analysis should be considered. In particular, the summary odds ratio we found should be interpreted with caution as the quantitative analyses indicated substantial heterogeneity.

## 5. Conclusions

In conclusion, this systematic review and meta-analysis provides evidence that participants of 65 years and older treated with PIPs are more at risk of adverse health outcomes than those using no PIPs,

including greater risks of falls, functional disabilities, unplanned hospitalizations, and mortality. Future studies should confirm these potential adverse effects of PIPs using larger longitudinal studies with an updated list of PIMs, and using non-pharmacological interventions as a comparator, including psychotherapy, social support, and lifestyle modifications. This knowledge will enable healthcare professionals to make informed decisions regarding the appropriate use of these medications in older adults. It will be also important to investigate the underlying reasons behind the use of PIPs, such as the prevalence of mental health disorders, social isolation, or inadequate access to alternative treatments. Understanding these factors will help develop targeted interventions and prevention strategies. Results of the present systematic review and meta-analysis provide additional evidence for an appropriate and safe use of psychotropics in older adults.

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## Ethical standards

The study was conducted in accordance with the ethical standards set forth in the Helsinki Declaration (1983).

## Conflict of interest

The authors identified no conflicts of interest.

## Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. No protocol has been prepared and registered.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jnha.2024.100187>.

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